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# Accepted Manuscript

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**Isolating response inhibition in the brain:  
Parietal vs. frontal contribution**

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## 1. Introduction

Response inhibition is a major cognitive-motor effortful process, in the realm of executive control, which has been extensively studied over the years (see Dempster, 1995, for a historical perspective). Nevertheless, inhibition is still a very broad term, and taxonomy of inhibitory processes is a matter of continuous debate (Aron, 2011; Diamond, 2014; Friedman and Miyake, 2004; Harnishfeger, 1995; Nigg, 2000). One such important process is the inhibition of a prepotent response, which is a well-defined construct within the wide range of inhibition-related processes (MacLeod et al., 2003). It is of particular interest because it plays a key role in cognitive development (Williams, Ponesse, Schachar, Logan, & Tannock, 1999) and is associated with age-related declines (Kramer, Humphrey, Larish, Logan, & Strayer, 1994). Moreover, deficits in inhibition of a prepotent response had been suggested as a hallmark of psychopathologies such as attention-deficit/hyperactivity disorder (ADHD, Barkley, 1997; Nigg, 2001; Wright et al., 2014), schizophrenia (Lipszyc & Schachar, 2010), and obsessive-compulsive disorder (OCD, e.g. Tolin et al., 2014).

A classical experimental task used to invoke response inhibition is the Go/No-go task (Donders, 1969) in which participants are instructed to make speeded responses to a specific Go stimulus, while withholding response to any other stimuli. Critically, the percentage of Go trials in the task ought to be larger than No-go, in order to build up a prepotent tendency to respond (Casey et al., 1997). This prepotent tendency is augmented if the task is simple, such that it triggers fast response latencies. The combination of a bias to respond and fast response times increases the demand for inhibition when No-go stimuli are presented. In some cases, these challenging conditions yield erroneous responses, which are termed commission errors (or false alarms). The rate of commission errors is typically used as a behavioral/neuropsychological index of a participant's proficiency of response inhibition (i.e., a low error rate indicates high inhibition capability).

A closely related experimental paradigm is the Stop-Signal Task (Logan, 1994; Verbruggen & Logan, 2008a). In this task, responses are made on every trial (typically a two-alternative forced choice is required in response to visual stimuli), unless a Stop signal (e.g. an auditory tone) is presented. The time interval between the presentation of the visual Go stimulus and the presentation of the Stop signal is varied, in an adaptive procedure. The experimental paradigm is specifically designed to stretch the difficulty of the task by gradually delaying the Stop signal. The time in which a subject is able to cancel a response – "Stop-Signal reaction time" (SSRT) – is

used as an index of inhibition capability. In other words, the Stop-Signal task measures how far into the motor response planning and execution processes, the response can still be stopped.

Indeed, both the Stop-Signal task and the Go/No-go task require inhibition of a prepotent response: they entail suppression of a motor action, where the action is deemed inappropriate. However, although they are sometimes treated interchangeably (e.g. Aron and Poldrack, 2005; Nigg, 2000), it could be argued that they do not tap the exact same mental mechanism. Using the terminology of Schachar and colleagues (Schachar et al., 2007; Verbruggen & Logan, 2008b) - while the Go/No-go task requires action restraining, the Stop-Signal task requires action cancellation. Previous findings have demonstrated that these processes are behaviorally distinct (Schachar et al., 2007) and have different developmental trajectories (Johnstone et al., 2007). Furthermore, they share common neural substrates only to a limited extent (McNab et al., 2008; Rubia et al., 2001; Swick, Ashley, & Turken, 2011; Zheng, Oka, & Bokura, 2008), and have different neurochemical modulation (Eagle, Bari, & Robbins, 2008). Action cancellation involves a cognitive stopping mechanism, but is also heavily dependent on motor functioning in order to cancel the already initiated response. Thus, the SSRT measure in the Stop-Signal task reflects the combination of cognitive and motor stopping abilities. In contrast, the process of action restraint is mainly cognitive, and the motor challenge in restraint tasks is small. Thus, commission error rate in a Go/No-go task is a cleaner measure of the cognitive aspect of response inhibition, as compared with SSRT in the Stop-Signal task.

Imaging studies that aimed to reveal the neural trace of response inhibition using Go/No-go and Stop-Signal tasks have suggested involvement of extensive brain regions: lateral frontal cortex (including superior, middle and inferior frontal gyri), the insula, the dorsal medial frontal cortex (including the supplementary and pre-supplementary motor areas), the anterior cingulate cortex, the inferior parietal cortex, the precuneus, as well as the striatum (see Criaud & Boulinguez, 2012; Swick, Ashley, & Turken, 2011 for informative meta-analyses). However, it is questionable whether all these regions are directly related to response inhibition, and attempts have been made to construct more specific hypotheses about the neural substrates of response inhibition.

The region drawing perhaps the most attention in this debate is the right inferior frontal cortex (hereafter rIFC). Based upon imaging studies of the Stop-Signal Task and lesion studies, Aron et al. claimed that response inhibition is localized in the right inferior frontal gyrus (rIFG; Aron et al., 2004). Recently, these authors have suggested a broader account, where rIFC is triggered by unexpected events and then generates inhibition by rIFC-based fronto-basal-ganglia networks

(Aron, Robbins, & Poldrack, 2014). One type of criticism about this view is concerned with the role of left IFC, which is belittled by Aron et al., despite evidence from left-lateralized patients regarding deficient Go/No-go performance (e.g. Krämer et al., 2013; Swick et al., 2008). The other type of criticism concerns the exact context in which rIFC is activated: some authors have demonstrated that rIFC is recruited not only when a prepotent motor response ought to be withheld, but also in other situations (discussed below) where inhibitory control is unnecessary (Swick & Chatham, 2014). Similar debates occur about the role of anterior insula cortex (AIC) and the pre-supplementary motor area (pre-SMA) in response inhibition (e.g. Aron, 2011; Cai et al., 2014; Chambers et al., 2009; Mostofsky and Simmonds, 2008; Wager et al., 2005).

Attempts to clarify the latter issues were made by changing the interpretation of the 'Stop' signal in classic Stop-Signal task designs. For instance, the infrequent 'Stop' signal could indicate a repeated response ("double Go", Chatham et al., 2012), a unique response (Erika-Florence, Leech, & Hampshire, 2014; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010) or no change in the required action and so could be ignored (Sharp et al., 2010). These studies demonstrated that recruitment of prefrontal cortex and particularly of rIFG did not differ between these novel conditions and the classic stop-trials. Thus, it transpires that prefrontal regions are not triggered exclusively by the mere inhibition process, but instead may be engaged in the detection of unexpected stimuli, in context monitoring, or are related to attentional capture (Hampshire, 2015). Additional evidence for this claim comes from studies which used Go/No-go tasks and manipulated the frequencies of the two types of events (T S Braver, Barch, Gray, Molfese, & Snyder, 2001; Meffert, Hwang, Nolan, Chen, & Blair, 2016; Wijeakumar et al., 2015). These studies have shown that some of the prefrontal activation in Go/No-go tasks, traditionally claimed to reflect inhibitory processes, is actually attributed to the infrequency of the No-go events rather than to the inhibition process per se (i.e. these regions are activated to a similar degree towards the infrequent stimulus, regardless if the infrequent is the Go or the No-go).

The lack of specificity of prefrontal activation reported in these previous studies could be due to the experimental contrast used as a measure of inhibition-related brain activation. Particularly, in most of these studies the neural response related to No-go trials is contrasted with the response to Go trials (or Stop trials contrasted with Go trials, in a Stop-Signal task). Thus, the measured signal may capture several different mental processes besides inhibition. First, it captures differences in visual properties and processing of the stimuli. Second, this contrast may reflect the difference between motor-related brain activity in the case of response execution, as compared to the case of non-response. As such, the No-go vs. Go contrast is not suitable for disentangling the

neural traces of response inhibition from mechanisms of stimuli processing, motor planning, as well as motor execution.

In order to overcome these potential confounds, we created a design which focuses only on analyses of No-go related activations. We manipulated the ratio of Go/No-go stimuli, to create two variants of the task: in one condition, No-go trials are rare, occurring in 25% of trials. In the other condition, No-go trials are more frequent, occurring in 75% of trials. In the rare-No-go condition most stimuli require action, so participants tend to respond very often and rapidly. When a rare No-go stimulus appears, inhibition processes are called upon in order to restrain the prepotent response. In contrast with this case, the need for inhibition is diminished in the prevalent-No-go condition because participants are not biased towards responding. The present study uses a design similar to the procedure used by Meffert and colleagues (Meffert et al., 2016), as both experiments include rare and prevalent No-go conditions. However, our approach to data analysis is crucially different, since Meffert et al. used the problematic comparison of No-go trials with Go trials. The novelty of the current study is in contrasting the rare-No-go condition (“difficult inhibition”, overriding a prepotent response) with the prevalent-No-go condition (“easy inhibition”, no prepotent response), thereby isolating inhibition-related activity while keeping visual and motor components equal across conditions. We claim that the use of this contrast can isolate and pinpoint brain regions where neural processes of response inhibition take place.

This approach has clear strengths, yet it raises a couple of concerns. In the rare-No-go condition, the No-go stimuli are less expected and hence are surprising and more salient than in the prevalent-No-go condition. These differences are inherent to the design which aims to elicit a prepotent response, and thereby create a context where inhibition is highly demanding. As a result, the No-go signal must be unexpected. Therefore, differences in expectation and in the level of surprise or saliency are unavoidable when comparing No-go trials taken from experimental conditions with different No-go probabilities and it is consequently expected that brain regions that are sensitive to salience will be active in such a comparison. In order to distinguish between brain activations that reflect inhibition from brain activations that derive from the effects discussed above, we examined an analogous contrast based on the Go trials. By subtracting prevalent-Go trials from rare-Go trials and examining the overlap with the results of our main contrast - prevalent-No-go subtracted from rare-No-go, we can identify brain regions that are activated towards rare stimuli in general, regardless of stimuli type (i.e. Go or No-go). These regions, activated more towards rare stimuli than towards prevalent stimuli, are likely to be involved in saliency detection, violation of expectation, or attentional capture. On the other hand,

regions where activation is unique to the rare-No-go vs. prevalent-No-go contrast are likely to be related to the inhibition process itself.

A whole brain approach was undertaken in order to expand the search beyond the obvious suspect regions - IFG/AIC/pre-SMA, and to mark new candidate regions which take part in response inhibition. Such regions may later be used as neural markers, to investigate atypicalities of response inhibition, which have been markedly reported in several neuropsychiatric disorders, as previously described.

## **2. Methods**

### **2.1 Participants**

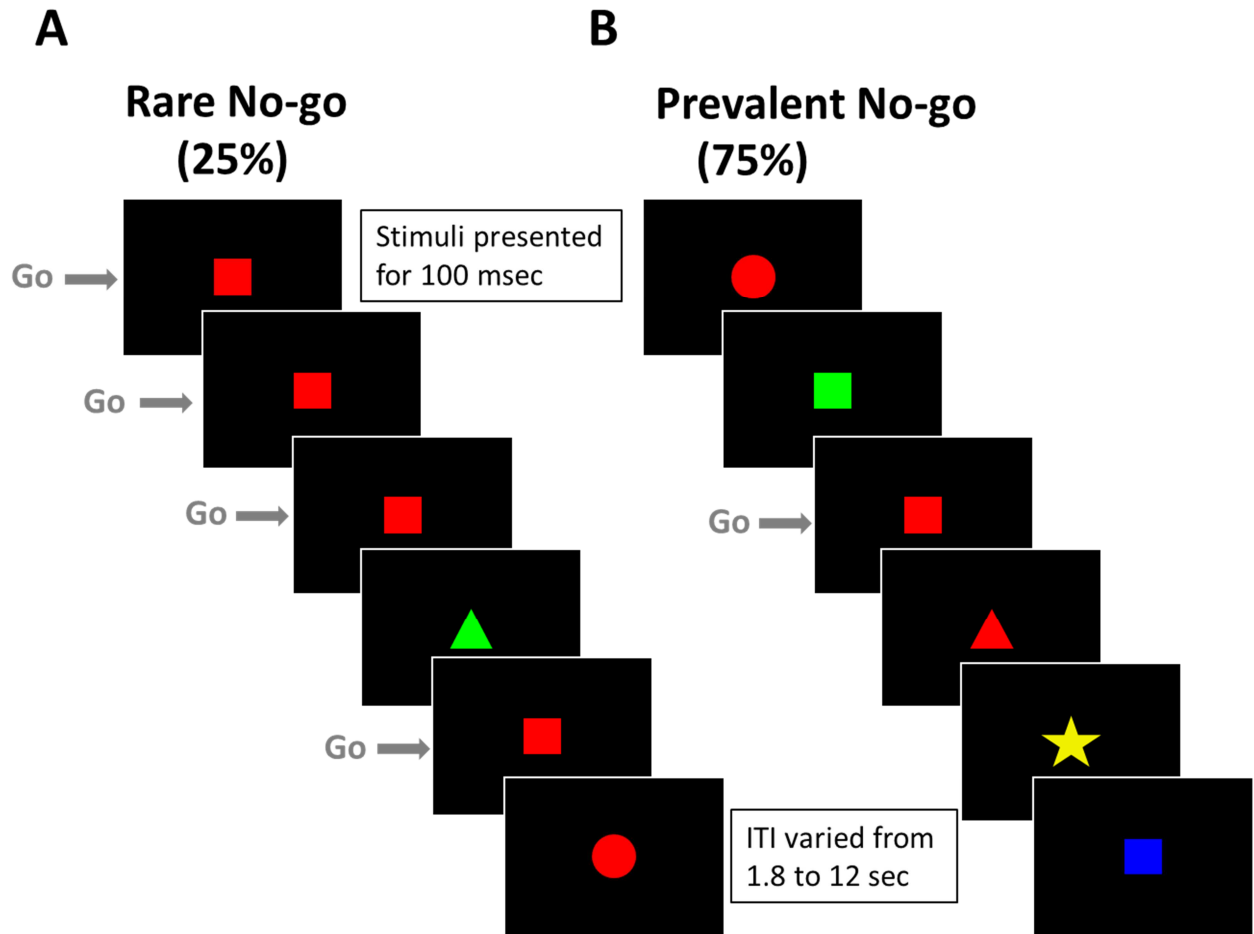
23 healthy volunteers (8 men and 15 women) aged between 19 and 37 participated in the study. All were right-handed with normal or corrected vision (glasses were replaced in the scanner with MRI-compatible goggles). Participants had no prior history of neurological or psychiatric disorders, no learning disability, and no contraindication to MRI scanning. To assure the absence of attention difficulties, participants completed the Adult ADHD Self-Report Scale (ASRS), a short screening scale for use in the general population (Kessler et al., 2005). All Participants scored within 1 SD of normal population's mean, as reported for the Hebrew version (Zohar & Konfortes, 2010). Three participants were excluded from the analysis: two due to a technical failure in the scanner, and the third due to excessive movement in the scanner (over 2mm). This resulted in a final sample of 20 participants (7 men, 13 women; mean age 27.4, SD 4.5). The study conformed to the Declaration of Helsinki and was approved by the ethics committees of Sheeba medical center and of Tel-Aviv University in Israel. All participants provided written informed consent.

### **2.2 Go/No-go task**

Participants were instructed to respond quickly when a Go stimulus - a red square - was presented in the center of a screen, and to withhold response to all other stimuli. No-go stimuli in the task were squares in other colors (blue, green, or yellow), red shapes other than squares (a circle, a triangle, or a star), or other shapes in other colors (all possible combinations of the shapes and colors mentioned above). We are mostly interested in No-go trials, where participants must withhold response. We used two variants of the task: rare-No-go and prevalent-No-go. In the rare-No-go condition, 75% of trials were Go trials and only 25% were No-go trials. In this case,



the participant is responding in most trials, and the demand for withholding a response when the rare No-go trials occur is high. In the prevalent-No-go condition the ratio is inverted – 25% of trials are Go trials and 75% are No-go trials. In this condition, there is no bias to respond; hence the need for inhibition is greatly reduced. In both conditions 1/3 of the No-go trials were same-color different-shape items, 1/3 were same-shape different-color items, and 1/3 were different-shape different-color items (which shared neither shape nor color with the Go stimulus). Each stimulus was presented centrally on its own for 100 msec, and the inter-stimulus-interval (ISI) varied from 1.8 s to 12 s, with a mean ISI of 2.75 sec. Stimuli and ISI's were randomly intermixed throughout the block, with a constraint of no more than 3 rare events consecutively (e.g. in the rare-No-go condition, there could not be more than three No-go stimuli one after another). A graphical description of the task is presented in Figure 1. Each block consisted of 164 trials, and lasted a total of 8 minutes. Reaction times (RT) were recorded from the onset of the stimulus, and average RT as well as standard deviation of RT were computed for correct responses only. Accuracy measures included the rate of omission errors (misses) and the rate of commission errors (false alarms). The latter serves as the main performance index of response inhibition.



**Fig. 1.** Experimental design. Illustration of the Go/No-go task, in which participants were shown a series of stimuli. Participants were instructed to respond quickly when a Go stimulus - a red square - was presented in the center of a screen, and to withhold response to all other stimuli. Trials occurred in a randomized order within two types of blocks: A) Rare-No-go (25% No-go stimuli and 75% Go stimuli) and B) Prevalent-No-go (75% No-go stimuli and 25% Go stimuli). Each run consisted of 164 trials, a total of 4 runs, order of conditions counterbalanced across participants. See Methods section for a full description of the task.

### 2.3 Experimental procedure

Before attending the fMRI session, participants conducted the experimental task in laboratory environment, on a separate day, in order to get familiar with the task. During the fMRI scan, participants performed 4 runs of the task, two runs of rare-No-go and two runs of prevalent-No-go, interspersed by an anatomical T1-weighted scan. The order of block types (rare- and

prevalent-No-go) was counterbalanced across participants. After completion of the experimental runs, additional scans were acquired, which are not further described in the current paper: a functional resting state scan, a diffusion weighted scan, and functional runs of an additional task. The total period of time in the scanner was approximately 90 minutes. The stimuli were projected onto a screen and viewed by a mirror mounted on the head coil. Responses were collected via an MRI-compatible response box.

## 2.4 fMRI data acquisition

Images were acquired on a 3T MRI (Magnetom Prisma, Siemens Medical Inc., Erlangen, Germany) scanner at SCAN@TAU center in Tel-Aviv University, using a 64-channel head coil. While participants completed the Go/No-go task, 236 functional images were collected using a single-shot 2D gradient-echo echo-planar sequence with the following parameters: slice thickness = 3.6 mm, 33 transverse slices in ascending interleaved order, TR = 2 s, TE = 35 ms, flip angle = 90°, matrix 96 x 96, FOV = 192 mm, for a voxel-wise resolution of 2 x 2 x 3.6 mm. Additionally, an MPAGE (high-resolution T1-weighted anatomical scan) was collected. The parameters for MPAGE were the following: TR = 1.75 s, TE = 2.61 ms, T1 = 900ms, FOV = 220 x 220, matrix = 220 x 220, axial plane, slice thickness = 1 mm, 160 slices, for an isotropic voxel resolution of 1 mm<sup>3</sup>.

## 2.5 fMRI preprocessing and analysis

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl), version 5.0 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012)). The first 3 volumes from each scan were discarded to allow for T1 equilibrium effects. The last 3 volumes from each scan were discarded as well, due to high prevalence of subject movements in this time range (while stimuli were no longer presented). Structural scans were skull stripped using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>, Ségonne et al., 2004). Registration of the functional data to the high resolution structural image was carried out using the boundary based registration algorithm (BBR; Greve and Fischl, 2009). Registration of the high resolution structural image to standard (Montreal Neurological Institute (MNI)) space was carried out using FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) and was then further refined using FNIRT nonlinear registration (Andersson 2007a, 2007b). The following pre-statistics processing was applied to the functional data: motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of full-width-half-maximum of 5mm; grand-mean intensity normalization of the entire 4D dataset by a

single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with  $\sigma = 25.0$  s).

Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Standard GLM fitting was conducted for all subjects. The following events were modeled in each run using a boxcar regressor convolved with a canonical double gamma hemodynamic response function: correct Go, correct No-go, omissions, and commission errors. Null events were not modeled and therefore constitute an implicit baseline. Events were modeled at the time of stimulus onset with duration of 0.1 s. The six motion parameters and temporal derivatives of all regressors were included as covariates of no interest to improve statistical sensitivity. The second level analysis, combining runs within subject, was carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). In order to isolate inhibition-specific activation, a *rare-No-go minus prevalent-No-go* contrast was computed for each subject. As described above, response inhibition is highly challenging in the rare-No-go, but substantially less so in the prevalent-No-go. Hence the contrast between No-go events in the two conditions reflects the inhibitory process. Additionally, a *rare-Go minus prevalent-Go* contrast was computed and overlapped with the latter contrast. The purpose of this procedure was to differentiate shared brain regions across the above Go and No-go contrasts showing increased activity when infrequent stimuli in general are presented, from brain regions showing increased activity particularly when rare-No-go stimuli are presented and inhibition is called upon.

Group analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by  $Z > 2.3$  and a (corrected) cluster significance threshold of  $P = 0.05$  (Worsley, 2001). Activation clusters are reported in MNI coordinates, using Cluster command in FSL. For visualization of results, statistical maps were projected onto an average cortical surface with the use of multifiducial mapping using CARET software (Van Essen, 2005)

(<http://brainvis.wustl.edu/wiki/index.php/Caret:Download>).

To verify that the results are not driven from the mere difference in the number of trials included in each regressor (number of No-go trials in the prevalent-No-go condition was 3 times the number of No-go trials in the rare-No-go condition), we repeated the analysis while listing only a random selection of 1/3 of the prevalent-No-go trials in the No-go regressor, and including an

additional regressor for the rest of No-go trials, which was not used in the next level of analysis. All other details of analysis were as previously described. We repeated this procedure five times, to verify that results do not depend on a specific selection of trials.

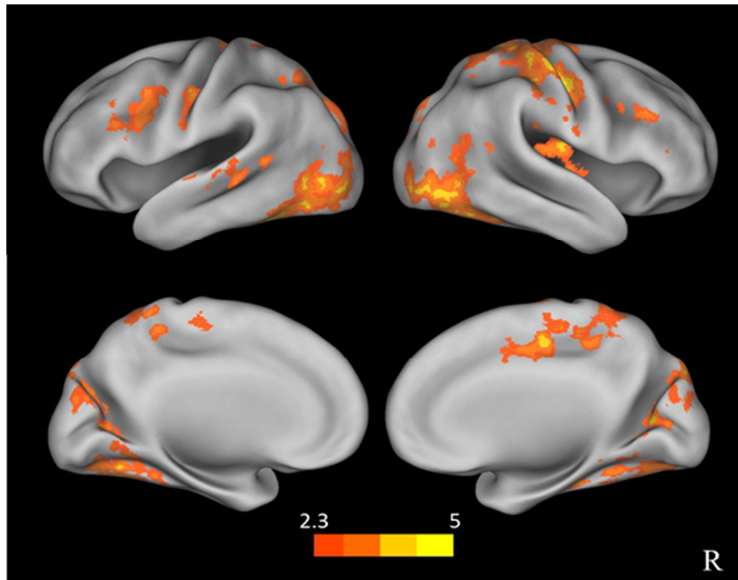
### 3. Results

#### 3.1 Behavioral results

Behavioral data were examined using paired samples t-tests. Reaction times for Go trials were significantly faster in the rare-No-go condition (493 ms) as compared with the prevalent-No-go condition (539 ms;  $t(19) = -6.55$ ,  $p < 0.001$ , Cohen's  $d = 0.77$ ). This reflects the increased tendency to respond in the rare-No-go condition. Commission errors were significantly more prevalent in this condition (average of 4% vs. 0.4%, in the rare-No-go vs. prevalent-No-go, respectively;  $t(19) = 5.92$ ,  $p < 0.001$ , Cohen's  $d = 1.76$ ), indicating that inhibition was indeed more demanding in the rare-No-go condition. The standard deviation of reaction times did not differ between conditions (62 ms and 56 ms, in the rare-No-go and the prevalent-No-go, respectively), indicating similar levels of sustained attention (Johnson et al., 2007; Shalev, Ben-Simon, Mevorach, Cohen, & Tsal, 2011). Omission errors were negligible (1% in both conditions). These results confirm our predictions, assuring that task selection has been appropriate, and that the frequency manipulation successfully creates a "difficult inhibition" condition (rare-No-go) and an "easy inhibition" condition (prevalent-No-go).

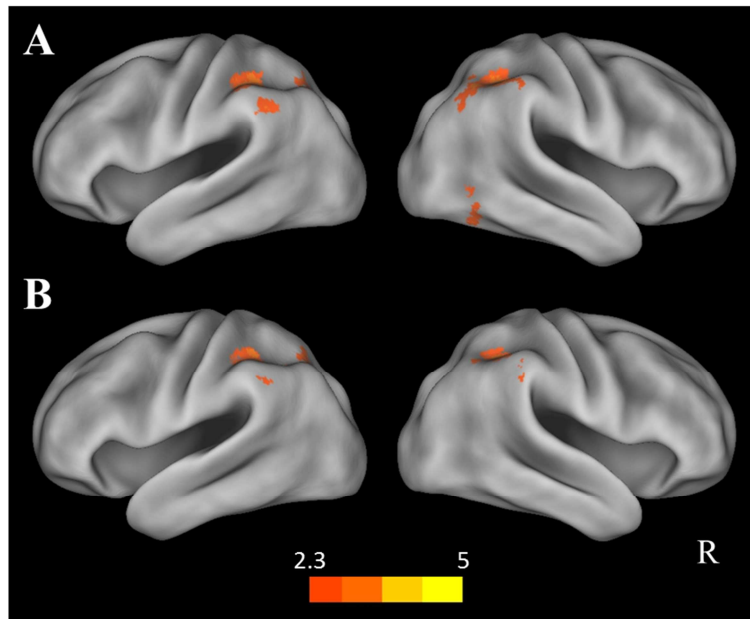
#### 3.2 fMRI results

Although our experiment was designed for contrasting rare-No-go trials vs. prevalent-No-go trials, we first wanted to make sure that the data is compatible with previous studies in the literature. To this end, we applied the classical contrast of No-go vs. Go trials in the rare-No-go condition. In line with the extensive literature, this contrast yielded activation in bilateral IFG, as part of a widespread fronto-parietal activation (see Figure 2 and Table 1), including middle frontal gyrus, bilateral dorsolateral prefrontal cortex (DLPFC) and right superior parietal lobule. In addition, widespread activation was obtained in bilateral occipito-temporal regions. However, as was explained earlier, various cognitive, perceptual and motor mechanisms could have been confounding this classical contrast.



**Fig. 2.** Activation in the classical contrast: No-go vs. Go. Widespread fronto-parietal activation, including bilateral IFG, middle frontal gyrus, dorsolateral prefrontal cortex and right superior parietal lobule. Statistical maps are corrected for whole-brain multiple comparisons and projected onto an average cortical surface using CARET (R=Right). The color represents the z-score.

In order to isolate brain activity which is uniquely associated with inhibition we used the contrast of No-go trials from the two different occurrence rates: the response to prevalent-No-go trials was subtracted from the response to rare-No-go trials. This contrast yielded clusters of activation in parietal regions, including the right and left intraparietal sulcus (IPS), in the left temporo-parietal junction (TPJ), and also in the right inferior temporal gyrus (see Fig 3A and Table 1). It is interesting to note that these clusters are partially overlapping with the results of the traditional contrast, but clearly they are much more localized. In addition, activation in the IPS and in the TPJ occurred also in segments which were not revealed in the traditional contrast.



**Fig. 3.** Activation for Rare-No-go vs. Prevalent-No-go (A) where all trials are included in the analysis (B) where the number of trials is equal across conditions. The figure presents one result out of five repetitions of the analysis (see more details in the Results, section 3.2). Significant activation was obtained in bilateral IPS and in left TPJ in both analyses. Statistical maps are corrected for whole-brain multiple comparisons and projected onto an average cortical surface using CARET (R=Right). The color represents the z-score.

**Table 1.** Clusters of activation.

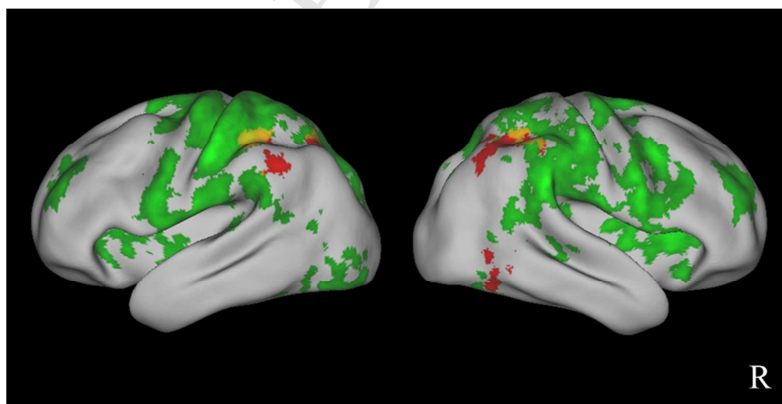
Brain region	Hemisphere	N voxels	Max Z-stat	x	y	z
<i>[No-go minus Go] in the rare-No-go condition</i>						
Lateral occipital cortex, occipital fusiform gyrus, temporal-occipital fusiform gyrus, inferior temporal gyrus, cuneal cortex, central opercular cortex (R), insular cortex (R), angular gyrus (R), middle temporal gyrus (R)	R/L	81,463	4.7	-47	-53	-14
Precentral gyrus, postcentral gyrus, superior parietal lobule, precuneous, juxtapositional lobule (R)	R/L	49,201	4.7	51	-17	57
IFG, middle frontal gyrus, precentral gyrus, postcentral gyrus	L	10,068	3.9	-48	13	38
IFG, middle frontal gyrus, precentral gyrus	R	4,396	3.8	55	32	23
Superior temporal gyrus, middle temporal gyrus, Central opercular cortex	L	2,594	3.4	-51	-33	3

*[rare-No-go minus prevalent-No-go]*

IPS	R	8,187	3.7	43	-49	50
IPS	L	2,126	3.3	-38	-42	48
TPJ	L	5,835	4.0	-43	-43	43
Inferior temporal gyrus	R	2,070	3.3	50	-51	-8

N Voxels: number of activated voxels per cluster; Max Z-stat: maximum  $z$ -statistic for each cluster;  $x$ ,  $y$ , and  $z$  are MNI coordinates for the peak of each cluster. R= right; L= left. IFG=inferior frontal gyrus; IPS=intraparietal sulcus; TPJ=temporoparietal junction.

Next, in order to identify and disregard regions involved in the identification of infrequent stimuli irrespective of the need for inhibition, we computed an analogous contrast of the Go trials: the activity that was measured during the presentation of prevalent-Go trials was subtracted from the response for rare-Go trials, and then overlapped with the results of the main contrast of No-go trials (Fig 4). While the comparison of rare vs. prevalent Go trials resulted in a largely distributed network of activations, the conjunction of rare vs. prevalent contrasts across Go and No-go trials yielded activation in anterior portions of the IPS (yellow clusters in Fig 4a). Importantly, more posterior portions of the IPS, as well as regions in the TPJ and in right inferior temporal gyrus (red cluster in Fig 4a), were only activated in the rare-No-go vs. prevalent-No-go contrast, indicating involvement in inhibition per se.





**Fig. 4.** Ruling out a possible confound of stimulus frequency and highlighting inhibition-specific activation clusters. Contrasts of Rare vs. Prevalent stimuli, overlaid on a single image to illustrate overlap, with No-go contrast in red and Go contrast in green. Overlapping regions appear yellow, indicating response to infrequent stimuli irrespective of trial type (Go/No-go). Regions that appear pure red in the image represent unique activation towards rare-No-go, interpreted as reflecting inhibitory processes. Statistical maps were binarized and projected onto an average cortical surface using CARET (R=Right).

A subtle point to note regarding all the contrasts discussed previously is that they compare different numbers of trials. By definition, the number of trials in the prevalent condition is larger than in the rare condition by a factor of three, hence the activation revealed by subtraction of these conditions might be contaminated by power differences. In order to control for this possibility, we repeated the main analysis including only a subset of the prevalent No-go trials. At the 1<sup>st</sup> level analysis, we randomly selected 1/3 of the trials to be included in the No-go regressor, and listed all other No-go stimuli in an additional (fifth) regressor of no interest. On the next level of analysis we computed again the rare-No-go minus prevalent-No-go contrast, using only the first No-go regressor described above. To corroborate the findings and to confirm that results do not depend on a specific subsample of trials, this analysis was repeated five times, using a different random selection of trials in each repetition. A similar pattern of results was obtained throughout the analyses: activation in bilateral anterior segments of the IPS was replicated in all repetitions, whereas activation in the more posterior segment of left IPS and in the left TPJ was replicated in majority of repetitions but not in all (3/5 and 4/5, respectively). In opposed to that, activation in right inferior temporal regions, which was evident in the original analysis (using all the trials), did not appear in any of the repetitions. This analysis confirmed that the activation seen in the parietal cortex is indeed attributable to the fundamental difference in inhibitory demands between rare- and prevalent-No-go conditions, and ruled out the possibility that it reflects the varying statistical power in the different conditions (see Fig 3B). This modified analysis narrows down even more the localized results of the current study, highlighting the importance of bilateral IPS and of left TPJ in response inhibition.

## 4. Discussion

Brain imaging experiments typically utilize a differential signal, measured as a contrast between responses obtained under two different conditions, such that common components are subtracted out. However, when the contrasted conditions differ on a number of levels such as during Go and during No-go events, the outcome of subtraction between them reflects many differences which are not cancelled out in the subtraction (as demonstrated in our study, Figure 2). We argue that the classical difference between No-go and Go trials includes activation related to motor planning and execution in the response to Go stimuli, which is absent in the No-go trials. Furthermore, visual and perceptual differences between the No-go and Go signals are also reflected in the subtraction between them. Hence, we suggest that tracking inhibition-related signal should be based solely on No-go trials, where withholding of a response is the main cognitive challenge. Our experimental design extracts a differential signal by modulating the intensity of inhibition activity in the brain, such that activation under rare-No-go condition (where a prepotent response ought to be inhibited) is contrasted with activation under prevalent-No-go condition (which includes the same stimuli and requires the same null response). Since the need for inhibition is diminished when No-go events occur very often, this is an adequate baseline for extracting a clean differential signal of neural activity representing response inhibition. In this way, visual, perceptual, and motor properties of No-go trials are kept equal across conditions, while the demand for inhibition is substantially higher in the rare-No-go condition. Thus, contrasting rare-No-go trials with prevalent-No-go trials isolates inhibition-related activation.

Using this methodological approach, we were able to highlight in the current study the contribution of parietal regions to inhibition of a prepotent response. The clusters of activation obtained were spatially well-defined and focused, localized in bilateral IPS and in left TPJ. Although IPS and TPJ activations are briefly mentioned among other brain regions in some previous reports of response inhibition in fMRI (Bledowski et al., 2004; Chikazoe et al., 2009; Wager et al., 2005 for IPS involvement; Nakata et al., 2008; Rothmayr et al., 2011; Van der Meer et al., 2011 for TPJ), it has not been consistent across studies and did not attract much attention in the response inhibition debate, which tends to revolve mainly around frontal regions. This seemingly inconsistency of our results with previous findings is likely attributed to the general differences between the classic approach and the current one, as explained earlier. Thus, by manipulating the frequency of Go and No-go stimuli, we were able to reveal the role of IPS and TPJ in inhibition, which was overlooked by previous studies.

Moreover, results were validated by an additional analysis equating the number of trials accounted for in each condition. This kind of analysis is important because statistical power increases as the number of trials per subject is increased. When conditions differ in the number of trials, they differ also in statistical power. Therefore, activation in contrasts such as rare- vs. prevalent-No-go (as in the current study) or No-go vs. Go (as in classic experiments), might reflect power differences rather than mere differences in cognitive processes. In order to overcome this potential bias, we applied a technique of sub-sampling the trials in the frequent condition. While this method is not common in fMRI experiments, it is well established in EEG (Luck, 2014). This analysis further assures the specificity and validity of the activation in the parietal cortex that was recorded in the current experiment.

One potential limitation of the present design (which is also relevant for previous studies assessing the classical contrast of No-go vs. Go) is that our frequency manipulation may have also affected the relative salience of the No-go trials. Stimuli can be salient due to either perceptual properties, novelty of the stimulus, unattended location, and most importantly for the current investigation – saliency can arise from low frequency of the stimuli and/or from violation of expectation. Indeed, both IPS and TPJ have been previously suggested to be involved in detection and processing of salient stimuli (Boehler, Appelbaum, Krebs, Chen, & Woldorff, 2011; Corbetta & Shulman, 2002; Downar, Crawley, Mikulis, & Davis, 2002; Geng & Mangun, 2008; Indovina & MacAluso, 2007; Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005; Mevorach, Shalev, Allen, & Humphreys, 2009) but also with its suppression (DiQuattro & Geng, 2011; Mevorach, Hodson, Allen, Shalev, & Humphreys, 2010). It has also specifically been shown that inferior parietal activation is modulated by probability and expectation (Doricchi, MacCi, Silvetti, & MacAluso, 2010; Vink, Kaldewaij, Zandbelt, Pas, & du Plessis, 2015; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013). However, in the case of prepotent responses, it is hard to disentangle inhibition from saliency and expectation, because the No-go stimuli ought to be unexpected and salient in order to challenge inhibition. In the current experiment, No-go trials in the rare-No-go condition are less expected than in the prevalent-No-go condition, and hence possibly more salient. Therefore, it could be argued that the activation detected in the IPS/TPJ in the current study reflects stimulus-driven orienting of attention or modulation of expectation rather than the implementation of response inhibition. To rule out this alternative account of the current findings, in an additional analysis we identified brain regions responding to saliency by looking at the response to rare stimuli in general: rare-Go trials and rare-No-go trials, and comparing it to the response to prevalent-Go and prevalent-No-go, respectively. The analysis demonstrated that the left TPJ and posterior right IPS, as well as some

smaller clusters in anterior right IPS and in left IPS, are uniquely modulated by the demand for inhibition and do not respond more to rare salient stimuli when they do not require inhibition. Thus, we conclude that while rare-No-go stimuli are indeed salient, the effects we identified are attributable to inhibition over and above a possible sensitivity of the reported brain regions to salience or expectancy.

Among many other attention functions previously associated with the parietal cortex (c.f. Wojciulik and Kanwisher, 1999), of particular relevance to the current study are findings relating IPS and TPJ activity to interference control and conflict resolution (Chmielewski & Beste, 2016; Derrfuss, Brass, Neumann, & von Cramon, 2005; Mecklinger, Weber, Gunter, & Engle, 2003; Zysset, Müller, Lohmann, & von Cramon, 2001). Interference control is sometimes described in terms of perceptual inhibition: inhibition of irrelevant distractors, or inhibition of irrelevant dimensions of a stimulus. While these accounts of inhibition are clearly distinguished from inhibition of a prepotent response, it may be the case that these processes rely on shared neural mechanisms, and that the IPS and TPJ are implicated both in perceptual inhibition and in motor inhibition.

The role played by the IPS and TPJ here may also speak to the recent taxonomy of proactive and reactive control (Aron, 2011; Braver, 2012). The framework of dual-mechanisms of control (Braver, 2012) for instance, postulates a qualitative distinction between these two modes of control: proactive control is the maintenance of goal-relevant information that operates in an anticipatory manner during the task, whereas reactive control reflects transient stimulus-driven attention. In Stop-Signal tasks, a common interpretation is that proactive control governs the Go trials whereas reactive control takes action when Stop signal occurs (Cai et al., 2016; Zandbelt et al., 2013). When the probability of Stop signals is varied in these tasks, a higher rate of Stop trials results in slower reaction times for Go trials and in more successful stops (Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2009; Ramautar, Kok, & Ridderinkhof, 2004; Vink et al., 2005; Zandbelt & Vink, 2010). On the basis of these findings, it is claimed that higher prevalence of Stop trials engages more proactive control. However, it is not unequivocal that increased proactive processing in these scenarios is associated with inhibition per se. Indeed, even in the context of a stop-signal task it is hard to ascertain whether proactive processes (driven by pre-cues) that affect the action potentials prior to trial onset, are indicative of action inhibition or facilitation (e.g. Claffey, Sheldon, Stinear, Verbruggen, & Aron, 2010). It is also not clear that the occurrence of a rare no-Go trial is solely associated with a reactive process which does not incorporate (at least to some degree) pre-stimulus readiness to inhibit a response. This means that

the possible association between high probability stop signal trials and proactive inhibition cannot be easily generalized to the current study's paradigm, as the No-go trials in our task are not easily ascribed to either proactive or reactive schemes.

Perhaps it is therefore not surprising that the brain activations we report here are typically associated with both proactive (IPS) and reactive (TPJ) attention control (see also the distinction between dorsal and ventral attention networks; Corbetta & Shulman, 2002). The IPS has been previously demonstrated to be activated in proactive control (Mevorach, Humphreys, & Shalev, 2009) immediately before stimuli onset. On the other hand, left TPJ involvement has been speculated to engage in reactive control (DiQuattro & Geng, 2011). Therefore, while the proactive/reactive framework is highly relevant to the issue of inhibition, it is not quite clear how these terms should be applied to the current task, and the results are inconclusive in respect to this issue. Clearly, the specific role of the IPS and of TPJ in response inhibition, and the way it interacts with other brain circuits in the context of inhibition, is a matter for further exploration.

While parietal activations were evident in our results, frontal regions (IFG in particular) were conspicuously absent in the critical contrast we report in the current study. The IFG was, in fact, activated in our study too, but this activation was apparent when processing of No-go trials was compared with Go trials, in line with previous extensive literature. Importantly, however, it was not modulated by the extent of inhibitory demand – i.e., IFG activation for rare-No-go trials is similar to that of prevalent-No-go trials. The latter finding is consistent with the results of Meffert et al. (Meffert et al., 2016), who implemented a full factorial analysis including rare and prevalent Go and No-go conditions, and obtained a main effect of stimulus (No-go vs. Go) in the IFG, but not an interaction effect with frequency – indicating that IFG is activated more in No-go events than in Go events, but is not modulated by the frequency of trials (and therefore is not sensitive to the degree of inhibitory demand). However, while Meffert et al. interpret the invariance of IFG to frequency as a support for IFG involvement in inhibition, we argue that it weakens this view: response inhibition is defined in the current study as overriding of a prepotent response (e.g. Casey et al., 1997; Nigg, 2000). Thus, a brain region specifically related to inhibitory control should be showing greater activation in response to rare-No-go trials (where inhibitory demand is high) than to prevalent-No-go trials (where inhibitory demand is low). Such a difference has not been observed in the IFG, in either the current study or Meffert et al.'s study, and this contradicts the specificity of IFG activity in inhibitory control.

Additional evidence challenging the role of IFG in such inhibitory control comes from an important meta-analysis by Criaud & Boulinguez (Criaud & Boulinguez, 2012), where Go/No-go

studies using equiprobable stimuli (50% Go and 50% No-go trials) were compared to studies using low probability of No-go stimuli. The results of the meta-analysis revealed no effect of No-Go probability in the IFG, i.e. its activation is similar in studies where No-go events are equiprobable (50%) and in studies where No-go events are rare (<50%). There again, if the IFG was implicated in response inhibition per se, it should have been activated to a lesser extent in the equiprobable designs, where the tendency to respond is diminished. Together with the current results, these findings support the claim that the IFG is not a module of response inhibition, but rather is involved in more general cognitive processes occurring in Go/No-go and Stop-Signal tasks. An influential alternative explanation to the findings of IFG activation to No-go/Stop events is that it belongs to domain-general regions of the cortex, which support a variety of novel or demanding tasks, sometimes referred to as the multiple-demand cortex or the task-activation ensemble (Cole & Schneider, 2007; Duncan, 2010; Fedorenko, Duncan, & Kanwisher, 2013; Hampshire & Sharp, 2015).

Another important point to be discussed is the selection of experimental tasks in the study of response inhibition. The meta-analysis by Criaud & Boulinguez (Criaud & Boulinguez, 2012) revealed that IFG is susceptible to effects of stimulus complexity and of working memory demands, and that this is the case also for the insula and for the pre-SMA. This, again, may fit with the idea of IFG in a multiple demand network rather than inhibition per se. This does not imply that all these regions do not play a role in response inhibition, but rather points out that task designs are often non-optimal for distinguishing response inhibition from other attentional mechanisms, and highlight the importance of task selection (see also Simmonds et al., 2008). In the current study we chose a simple version of a Go/No-go task (Shalev et al., 2011): the Go stimulus is unique and easily distinguishable from the No-go stimuli, and the mapping of stimuli to response is consistent (i.e. is not updated during the task according to previous trials), thus minimizing perceptual complexity and working memory load. This selection of a simple task, along with the manipulation of No-Go probability produce an appropriate design in order to pinpoint response inhibition, conforming to the recommendations of Criaud and Boulinguez, and is another advantage of the current study.

To conclude, the current study applies a novel approach for isolating response inhibition-related activity in neuroimaging, and suggests that bilateral IPS and left TPJ could be a markers of inhibitory control. In future studies this marker could be utilized to investigate atypicalities of response inhibition, and to further investigate the interaction of brain activity with behavioural measures and with symptoms of difficulty in response inhibition (i.e. impulsivity).

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## Conflict of interest statement

The authors declare no conflict of interest.

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